Accumulated Body Burden and Endogenous Release of Lead in Employees of a Lead Smelter

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Bone lead levels for 367 active and 14 retired lead smelter workers were measured *in vivo* by X-ray fluorescence in May–June 1994. The bone sites of study were the tibia and calcaneus; magnitudes of concentration were used to gauge lead body burden. Whole blood lead readings from the workers generated a cumulative blood lead index (CBLI) that approximated the level of lead exposure over time. Blood lead values for 204 of the 381 workers were gathered from workers returning from a 10-month work interruption that ended in 1991; their blood level values were compared to their tibia and calcaneus lead levels. The resulting relations allowed constraints to be placed on the endogenous release of lead from bone in smelter workers. Calcaneus lead levels were found to correlate strongly with those for tibia lead, and in a manner consistent with observations from other lead industry workers. Relations between bone lead concentration and CBLI demonstrated a distinctly nonlinear appearance. When the active population was divided by date of hire, a significant difference in the bone lead–CBLI slope emerged. After a correction to include the component of CBLI existing before the workers' employment at the smelter was made, this difference persisted. This implies that the transfer of lead from blood to bone in the workers has changed over time, possibly as a consequence of varying exposure conditions. *Key words:* blood lead indices, bone lead, occupational lead exposure, smelter workers, X-ray fluorescence. *Environ Health Perspect* 105:224-233(1997)

Lead is a commonly encountered metal that may have toxic effects upon inhalation or ingestion. In recent times, the removal of lead from gasoline and paint products has lowered the risk of exposure for the general public, but concern remains regarding certain environmentally or occupationally exposed groups. Blood lead monitoring is normally applied to workers who are routinely exposed to lead. This technique, however, reflects only recent exposure, since the half-life of lead in blood is approximately 30 days (*1*). Bone lead measurements, on the other hand, are more indicative of cumulative exposure history. With more than 90% of absorbed lead accumulating in bone (*2*), such measurements are critical to the understanding of both individual exposure histories and, more generally, lead kinetics within the body.

X-ray fluorescence is a noninvasive method of bone lead determination that relies on the excitation of characteristic lead X-rays (*3*). The introduction of ^{109}Cd as an excitation source, with 88 keV photons emitted from approximately 4% of its decays, has brought improved precision to bone lead quantitation (*4*). Systems incorporating this source have the additional advantages of self-normalization (yielding results in terms of the mass of lead present per unit mass of bone mineral) and insensitivity to variations in source to sample distance and overlying tissue thickness (*5*). The X-ray fluorescence apparatus used in this particular study incorporated various improvements in design, as detailed by Gordon et al. (*6*).

We examined a population consisting of both active and retired workers from a lead smelter. This site is operated by Brunswick Mining & Smelting, and is located in the province of New Brunswick, Canada. The plant has operated since 1966, and workers' whole blood lead measurements have been compiled by the smelter since 1968. Bone lead readings were performed on smelter employees during the months of May and June of 1994.

In previous studies of retired workers, a positive correlation has been observed between current whole blood lead and bone lead (*7,8*). These results imply that the release of lead from bone is a dominant source of retired workers' exposure. That such a strong correlation has not been evident among active workers suggests that endogenous exposure, while perhaps still present, is being overwhelmed by exogenous lead supply (inhaled or ingested lead). A 10-month strike at the smelter (from July 1990 to May 1991) provided an opportunity to test this hypothesis.

Following the resumption of work duties, blood lead readings were performed on all employees. These results and the subsequent 1994 bone lead measurements were examined to gauge the intensity of endogenous lead exposure for a typical smelter worker. The unique advantages of this survey lie in the large sample of workers involved and that these individuals would have been active smelter employees but for the disruption of labor. The latter point addresses the potential objection to results obtained from retired workers—that the endogenous exposures observed were partially a consequence of age-related bone store releases, and therefore were not applicable to the population in general. A smaller sample of retired Brunswick workers was also included in a similar analysis of endogenous lead contribution to total exposure.

A strong positive correlation has been noted in lead industry workers between bone lead concentrations at various bone sites (*9,10*). This study will examine bone lead levels for the tibia and calcaneus. The tibia is representative of compact, cortical bone, which makes up approximately 80% of skeletal mass. Of five skeletal sites investigated by Wittmers et al. (*11*), the tibia was deemed to be most representative of total skeletal lead burden. The calcaneus is predominantly trabecular bone, and would therefore be expected to exhibit a somewhat different pattern of lead metabolism (*8*).

Bone lead results were compared to a cumulative blood lead index (CBLI) in an

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attempt to derive a relation between these two long-term exposure markers (*12,13*). Because past levels of exposure were higher than current levels, the slope of this relation was examined as a function of time of hiring for the worker population. A difference in slope between groups selected by time of hiring might then be indicative of a change in the transfer efficiency of lead from whole blood to tissue. Such a variation in transfer would be consistent with existing conceptions of lead kinetics in the human body.

Materials and Methods

The worker population for which bone lead readings were performed consisted of 381 people; three females and 378 males. Of this total group of 381, a subset of 14 consisted of retired employees, all of whom were males of age 55 to 72 years. The ages of the active workers ranged from 22 to 63 years.

Prior to bone lead measurement, informed, written consent was obtained from all workers participating in the study. The tibia lead measurements were made at the mid point of the left tibial bone shaft, with a source-to-skin distance of about 2 cm. The calcaneus readings were taken from the lateral side of the right heel bone. Each procedure lasted approximately 30 min, resulting in a total effective dose of about 0.07 μSv (*14*). A high purity germanium detector was utilized to record the spectral distribution resulting from the ^{109}Cd photon interactions in the body. The three major components of the spectrum result from Compton scattering (with the geometry employed, E_γ = 66.5 keV), elastic scattering (E_γ = 88.0 keV), and the characteristic lead K X-ray peaks of various energies. These fluorescent peaks were fit by a Marquardt nonlinear routine, with the widths set equal to that of the elastic scatter peak. Characteristic X-ray peak to coherent peak ratios were calibrated against the same ratios determined from bone phantoms doped with known amounts of lead (*5*). The end product was a bone lead concentration from each worker's tibia and calcaneus, determined in units of microgram of lead per gram of bone mineral.

Following the strike, blood lead measurements were performed by smelter personnel on all workers, in most cases immediately upon an individual's return to work. To screen out workers whose blood leads were not reflective of mostly endogenous and background lead exposures, it was required that a blood lead reading for inclusion in this component of the study be carried out within 5 working days of the resumption of employment. In total, this resulted in a sample size of 204 employees. The bone lead values of these 204 workers were derived from the X-ray fluorescence measurements of 1994. A correction to this data was implemented to account for the slight increase in bone lead that would have occurred over the 3 years between the return to work and the bone lead readings. The magnitude of this correction was generated from the average rates of increase of bone lead concentration per year per unit blood lead concentration for the smelter workers. These constants for the tibia and calcaneus bone sites will be introduced below.

The time between whole blood lead measurements at Brunswick varies depending on the exposure history of each employee, but the sampling frequency generally ranges from once per month to once per year. A CBLI was constructed for each of the workers using the blood lead data provided by the smelter. Such an index is an integration of blood lead levels over a worker's employment time, and therefore provides a good approximation of the total exposure to lead (*15*).

The CBLI was calculated for each worker by integrating blood lead (BPb) readings over time via the trapezoidal rule:

$$CBLI = \int BPb\, dt = \Sigma 0.5\left(BPb_i + BPb_{i+1}\right)\Delta t$$

Here, BPb_i and BPb_{i+1} represent the i^{th} and $(i+1)^{th}$ measurements of blood lead, taken Δt years apart. A number of assumptions were necessary in order to determine realistic CBLI estimates. The starting point for

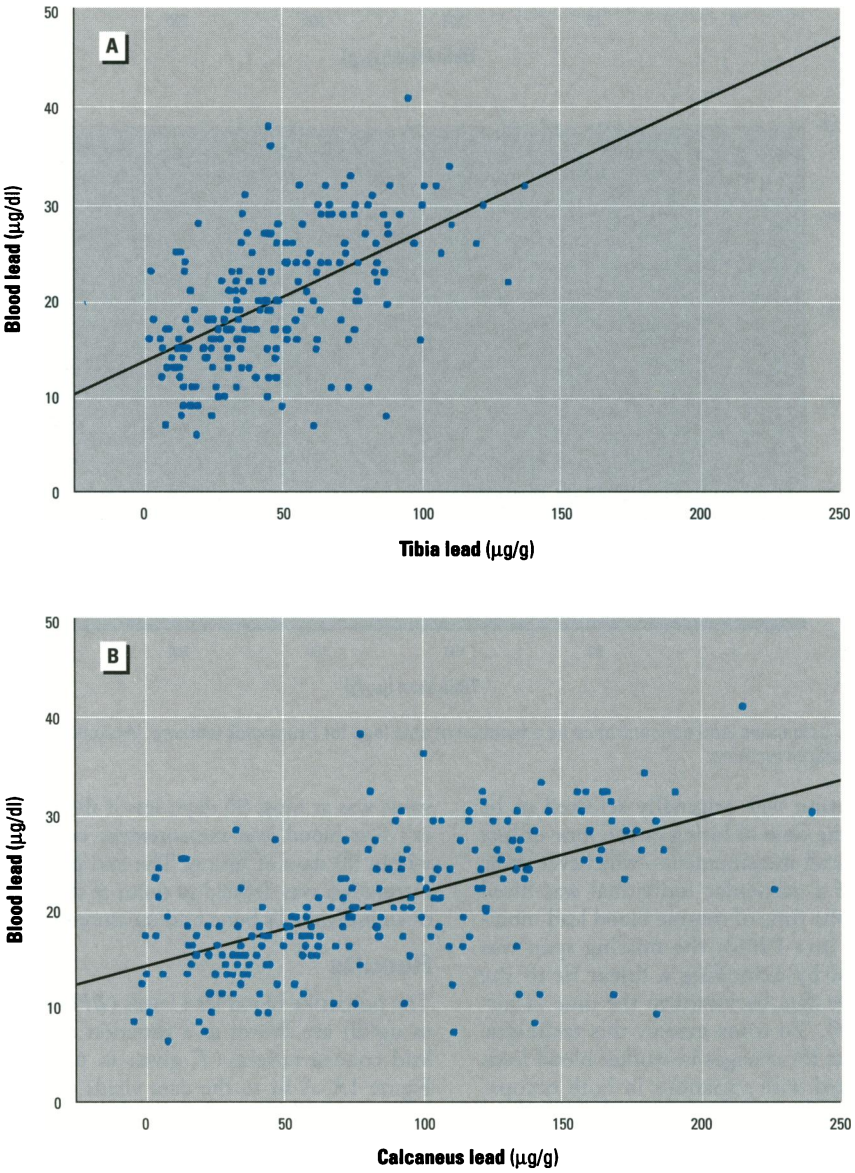

Figure 1. Blood lead levels as a function of bone lead concentration for workers returning following labor disruption. The blood lead levels reflect endogenous and background exposures to lead. (A) Blood lead as a function of tibia lead; (B) blood lead as a function of calcaneus lead.

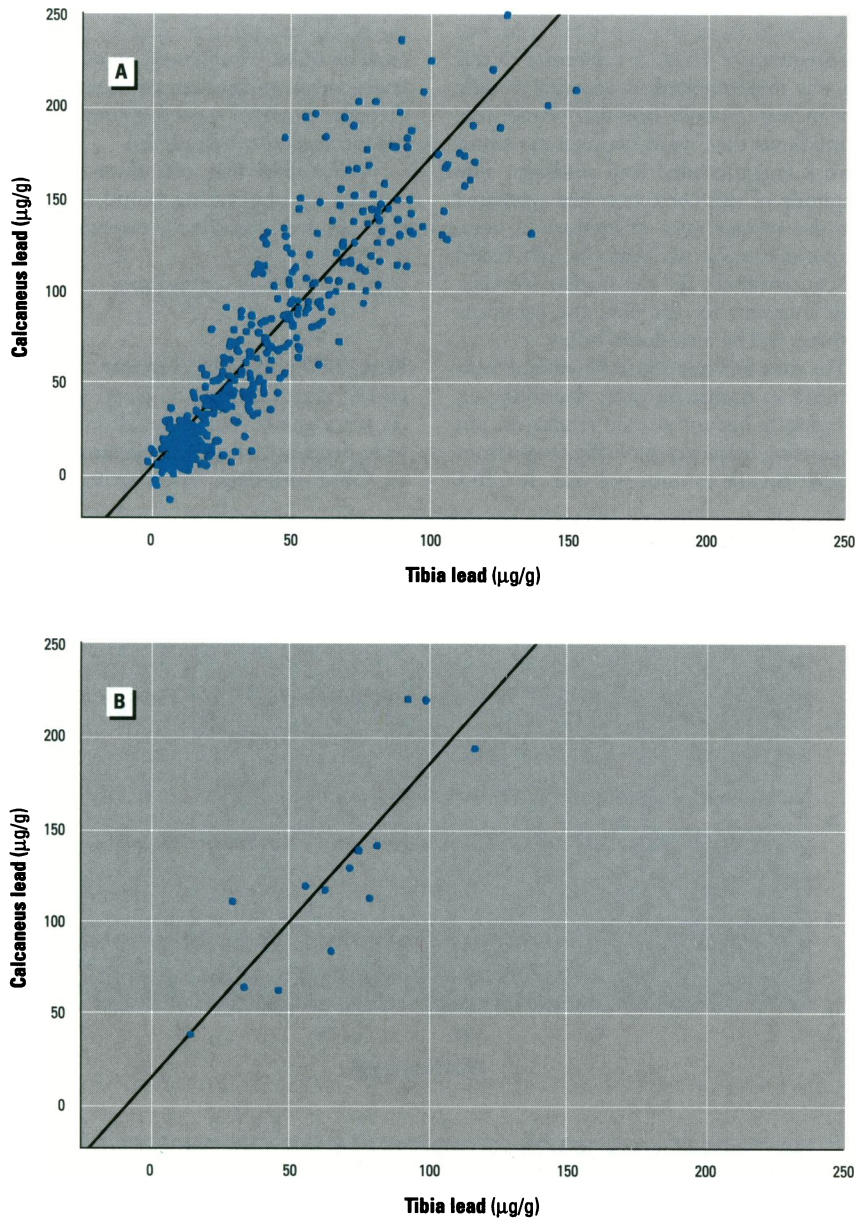

Figure 2. Calcaneus lead concentration as a function of tibia lead for Brunswick workers. (A) Active workers; (B) retired workers.

integration was originally selected to be either the time of hiring or the time of first blood lead measurement—whichever came first. If a particular individual was hired before the time of routine blood lead monitoring (pre-1968), the missing span was covered by extending a linear fit to the available data backward to the time of hiring (*16*). To some extent, this technique accounts for changes in worker blood leads associated with variations in both occupational and environmental exposures (*17*). In all cases, a period of adjustment was incorporated between a background blood lead level at hiring and the first blood lead level while working (*15*). The amount of time allocated to reach an equilibrium working value was at most 90 days; less if the worker's first blood lead measurement occurred within 90 days of hiring. The end point of integration was defined to occur at the time of an individual's bone lead measurement.

Results

The poststrike blood lead levels (*BPb*, given in µg/dl) are shown as a function of tibia lead concentrations (*T*, given in µg/g) in Figure 1A. A fit to the data yields the following line of regression:

$$BPb = (0.136 \pm 0.014)\,T + (13.6 \pm 0.8)$$

with a coefficient of determination (r^2) of 0.31 from a sample size (n) of 204 workers ($p<0.001$). A similar fit to the poststrike blood lead (*BPb*) versus calcaneus lead concentration (*C*, given in µg/g) data is also shown in Figure 1B. These results produced a best fit relation of

$$BPb = (0.0776 \pm 0.0074)\,C + (13.6 \pm 0.7)$$
$$[n = 204; r^2 = 0.35; p<0.001].$$

When the set of 14 retired Brunswick workers were analyzed in a similar fashion, the following relations provided the best fits to the data:

$$BPb = (0.162 \pm 0.051)\,T + (6.1 \pm 3.6)$$
$$[n = 14; r^2 = 0.46; p<0.01];$$

and

$$BPb = (0.0593 \pm 0.0305)\,C + (9.2 \pm 4.2)$$
$$[n = 14; r^2 = 0.24; p<0.08].$$

A linear regression was also applied to a comparison of workers' calcaneus and tibia bone lead levels. In such a relation, the tibia lead data is normally designated as the independent variable. This treatment is appropriate because a typical tibia lead measurement has more precision (~ ± 5 µg/g) than a calcaneus reading (~ ± 8 µg/g). In addition, tibia lead concentration is a more stable parameter over time because the calcaneus is more metabolically active. The complete set of results for current workers is illustrated in Figure 2A, with the following line of best fit superimposed:

$$C = (1.70 \pm 0.04)\,T + (0.6 \pm 2.2)$$
$$[n = 367; r^2 = 0.81; p<0.001].$$

For the retired Brunswick workers (results shown in Figure 2B), an analysis of the bone lead relation yields a fit such that

$$C = (1.70 \pm 0.29)\,T + (16.7 \pm 20.7)$$
$$[n = 14; r^2 = 0.74; p<0.001].$$

When tibia lead levels of occupationally exposed individuals are plotted against CBLI values, a linear relationship has been found to prevail over a variety of studies. These results, and those derived from measurements at other bone sites of interest, are summarized in Table 1. To derive a linear relation between the long-term indices of bone lead and CBLI, two complicating factors must be assumed negligible. The first is the common assumption that the blood lead contribution from bone is relatively small for workers subjected to heavy exogenous exposures. This assumption is a reasonable one for the smelter population, particularly for the tibia data, because the half-life of lead in predominantly cortical

bones (such as the tibia) is significantly longer than that in trabecular bones (*8*). A second important point implicit in the linear approximation is that the transfer efficiency of lead from blood to bone is to be taken as constant. This ignores potential variations in transfer caused by age, blood lead concentration, or source of lead (endogenous vs exogenous).

The relations between bone lead and CBLI for the active smelter workers are illustrated in Figures 3A and B. Although these results suggest a certain nonlinearity, a best fit linear relation has been determined between the parameters of bone lead (μg/g) and CBLI (y × μg/dl) via a least squares method. This permits a more direct comparison with results from previous studies. For the tibia, the resulting fit was of the following form (Fig. 3A):

$$T = (0.0556 \pm 0.0020)\,CBLI + (2 \pm 2)$$
$$[n = 367; r^2 = 0.69; p<0.001].$$

Entering the calcaneus lead data as a function of CBLI produced a more steeply rising slope, as shown in Figure 3B:

$$C = (0.111 \pm 0.003)\,CBLI - (9 \pm 3)$$
$$[n = 367; r^2 = 0.77; p<0.001].$$

These fitted slopes are similar to those obtained by Somervaille et al. (*13*), Cake (*16*) Hu et al. (*18*), and from other occupationally exposed populations (see Table 1).

A similar analysis may be applied to the subset of retired smelter workers. For the tibia lead–CBLI comparison (Fig. 4A), the best fit relation was determined as

$$T = (0.0700 \pm 0.0216)\,CBLI - (17 \pm 26)$$
$$[n = 14; r^2 = 0.47; p<0.01].$$

In turn, the calcaneus lead data as a function of CBLI(Fig. 4B) was best described by the following equation:

$$C = (0.144 \pm 0.041)\,CBLI - (42 \pm 50)$$
$$[n = 14; r^2 = 0.50; p<0.01].$$

Although retired workers demonstrate larger bone lead–CBLI slopes than active workers, the differences between the two populations are not statistically significant.

Figure 5 shows the mean blood lead levels from 1968 to 1995 of workers participating in the current study. There is a general decline in blood lead level over time, with the most marked decrease observed after about 1977. This decline in lead exposure was attributed to changes made at the smelter just prior to 1977 regarding working conditions, hygiene, and safety regula-

Table 1. Linear fits to bone lead–cumulative blood lead index relations for various bone sites in occupationally exposed populations

Industry	Bone site	*n*	Slope	*r*	Reference
Various	Phalanx	43	0.17**	0.41(r_s)	(*12*)
Battery	Tibia	88	0.060 ± 0.005#	0.82	(*13*)
Crystal glass	Tibia	79	0.050 ± 0.003#	0.86	(*13*)
Various	Tibia	12	0.061 ± 0.008#	0.92	(*18*)
Various	Patella	12	0.218 ± 0.026#	0.93	(*18*)
Refinery	Tibia	15	0.10 ± 0.02#	0.87	(*19*)
Refinery	Tibia	11	0.10 ± 0.02#	0.91	(*19*)
(Longitudinal)	Tibia	7	0.052 ± 0.021*	—	(*19*)
Battery	Tibia	91	0.028 ± 0.003#	0.67	(*7*)
Battery	Calcaneus	90	0.073 ± 0.013#	0.54	(*7*)
(Retired)	Tibia	13	0.061 ± 0.012#	0.79	(*7*)
(Retired)	Calcaneus	13	0.105 ± 0.018#	0.87	(*7*)
Smelter	Tibia	100	0.022#	0.60	(*8*)
Smelter	Calcaneus	100	0.042#	0.44	(*8*)
Recycling	Tibia	53	0.059 ± 0.009#	0.70	(*16*)
Recycling	Calcaneus	53	0.117 ± 0.018#	0.68	(*16*)
Smelter	Tibia	123	0.07# (log fit)	0.80	(*15*)

Abbreviations: *n*, number; *r*, regression coefficient.
*$p<0.1$; **$p<0.01$; #$p<0.001$.

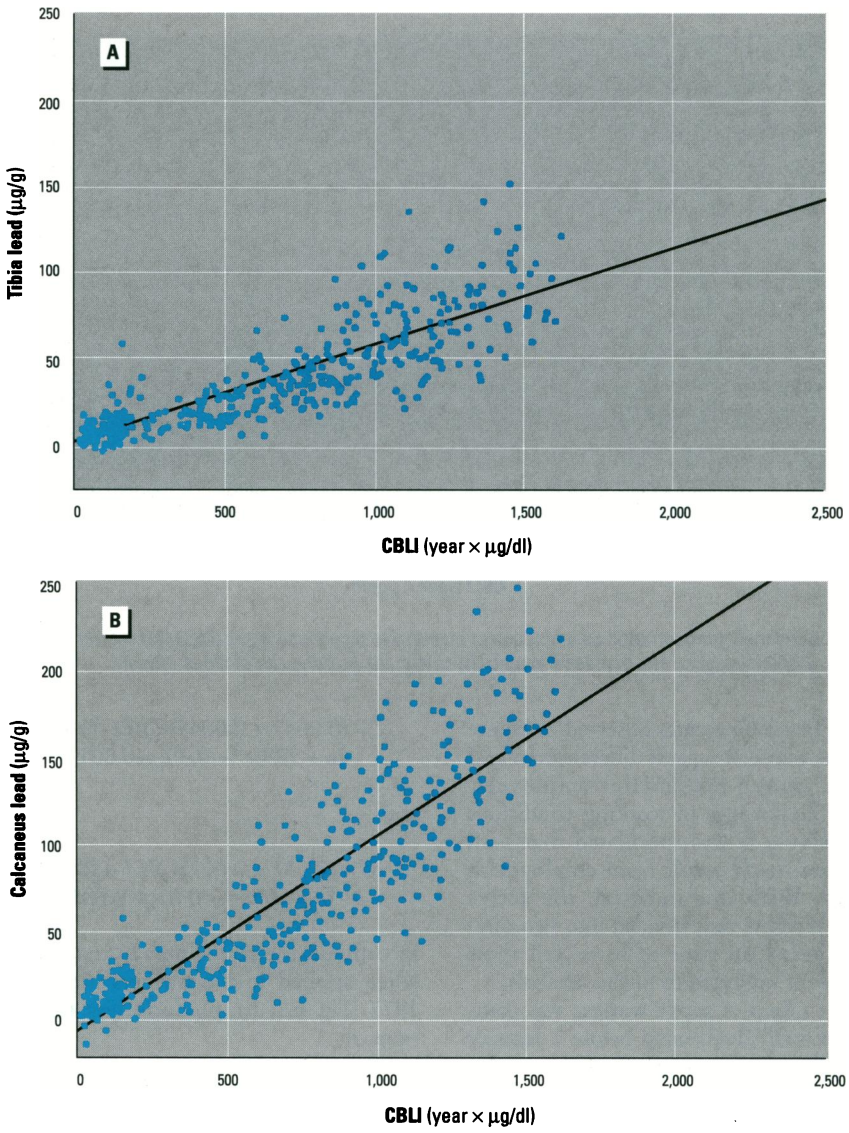

Figure 3. Bone lead concentration as a function of cumulative blood lead index (CBLI) for active smelter workers. (A) Tibia as bone site of measurement; (B) calcaneus as bone site of measurement.

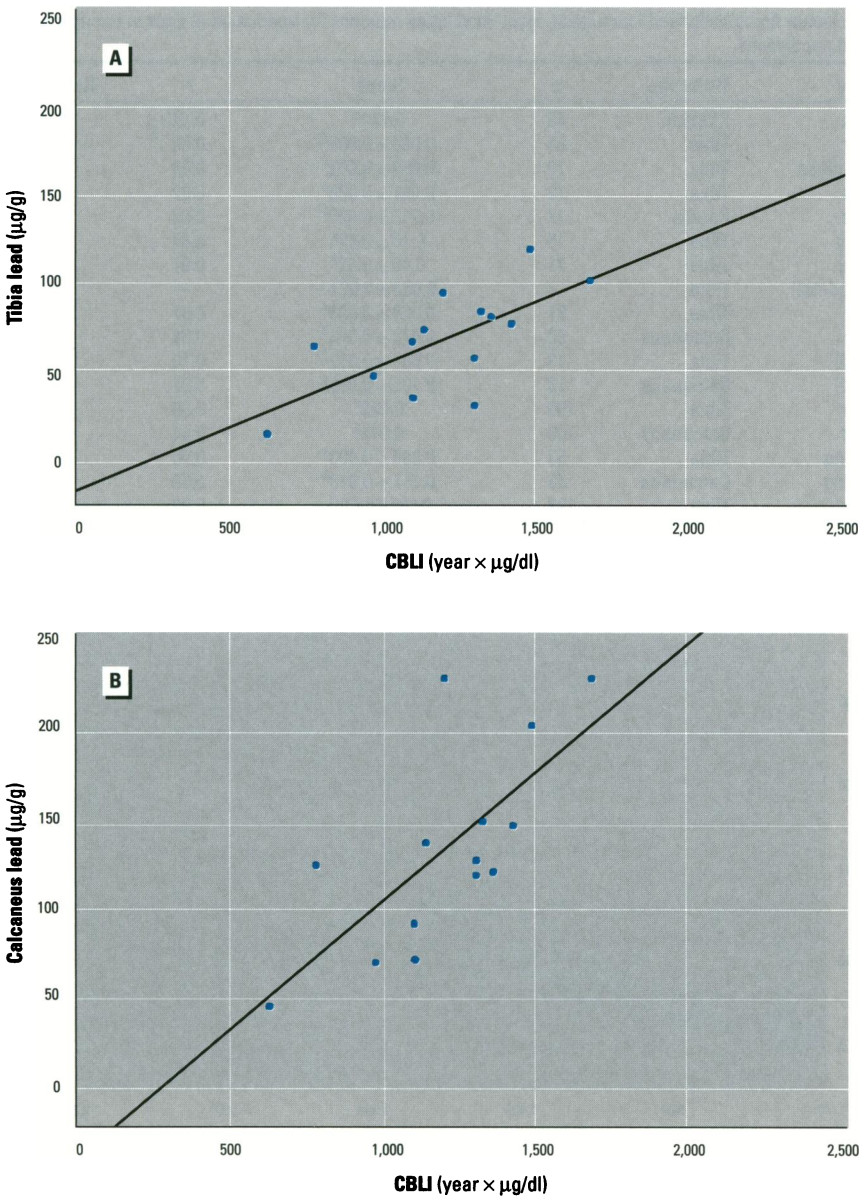

Figure 4. Bone lead concentration as a function of cumulative blood lead index (CBLI) for retired smelter workers. (A) Tibia as bone site of measurement; (B) calcaneus as bone site of measurement.

tions. The nonlinearities observed in Figure 3 (active workers) suggest differences in lead uptake among the smelter employees. Given the changes in working conditions noted above, it was speculated that such variations could result from employment history. With this in mind, the active smelter workers were divided into two categories based on time of hire, and their results were subjected to further analysis.

One subset of active workers was composed of individuals hired before 1 January 1977; the other consisted of those who began work after this date. The linear fits to the data for workers hired before 1977 (Fig. 6A,B) resulted in the following relations:

$$T = (0.0687 \pm 0.0049)\,CBLI - (13 \pm 5) \quad [n = 209; r^2 = 0.49; p<0.001];$$

and

$$C = (0.147 \pm 0.007)\,CBLI - (48 \pm 8) \quad [n = 209; r^2 = 0.65; p<0.001].$$

In contrast, the same linear fitting routine, when applied to the workers hired after 1977 (Fig. 6A, B), produces best fit equations of

$$T = (0.0466 \pm 0.0033)\,CBLI + (5 \pm 1) \quad [n = 158; r^2 = 0.57; p<0.001];$$

and

$$C = (0.101 \pm 0.006)\,CBLI - (1 \pm 2) \quad [n = 158; r^2 = 0.67; p<0.001].$$

The differences in slope between the two sets of workers are significant ($p<0.001$), with individuals more recently hired demonstrating more shallow bone lead–CBLI relations. It is of interest that the bone lead–CBLI relations of retired workers closely match those of active workers hired before 1977. Two explanations for these apparent variations in slope over time are immediately obvious, and will be considered in turn.

Variable transfer hypothesis. The differences in slope may be a product of some variation in the workers' transfer of lead from whole blood to bone. This explanation would suggest that the workers hired before 1977 have demonstrated a more efficient transfer of lead to bone than those more recently hired. This situation is designated the variable transfer hypothesis and is diagrammed in Figure 7. Here, the arrows represent efficiency of lead transfer from blood to bone. Potential causes of such a variation in tissue uptake per unit exposure will be discussed below. Note that the CBLI calculated over an individual's occupational history at the smelter is actually an underestimate of their lifetime CBLI. The lifetime CBLI would be a sum of the smelter CBLI and a presmelter CBLI. For the variable transfer explanation to be valid, therefore, one would have to demonstrate that the component of a typical individual's CBLI compiled before their occupational exposure to lead was not a contributing factor in producing the differences that are observed in slope.

Systematic bias hypothesis. Alternatively, the differences observed in slope may be mere artifacts of incomplete lifetime CBLI data. As a consequence of inflated background past lead exposures, it seems possible that the sample of workers hired before 1977 have smelter CBLI values that grossly underestimate their true lifetime CBLI. Conceivably, this could produce artificially steep bone lead–CBLI relations, particularly if the largest underestimations occurred for those workers who have spent the greatest amount of time at Brunswick. Conditions that could create such a systematic CBLI bias are illustrated in Figure 8. This scenario seems plausible, considering that blood lead levels for the general population were measurably higher in the past and have been decreasing steadily since the 1970s (*17*). The net effect of such a set of circumstances would be the illusion of a higher transfer efficiency to bone resulting solely from a bias in CBLI data. Even if the true efficiency of uptake had been exactly the same over

time (as illustrated by the arrows in Fig. 8), a comparison of the smelter CBLI to bone lead would suggest a significant difference.

Presmelter CBLI. To investigate which of these two potential explanations is more likely correct, it is necessary to calculate a presmelter CBLI component for each worker. A revised, or lifetime, CBLI may then be implemented to see if the differences between the two populations persist. In order to construct a worker's lifetime CBLI that includes presmelter contributions, certain assumptions must be introduced. A starting point in time for the integration is not a trivial question. The rapid turnover in bone exhibited throughout the childhood years renders the idealized treatment of bone as a long-term storage site of lead inappropriate. In this respect, a case could be made for beginning the revised CBLI postadolescence. This assumption is particularly appealing in the calculation of a lifetime CBLI for a lead industry worker, whose lead exposure before the age of employment would in most cases be negligible in comparison (*15*). Others would argue that the entire life history of lead exposure must be accounted for if both the CBLI and bone lead are to be used as chronic indices. This point of view would suggest that the revised CBLI should be extended to the time of birth (*18*).

We approached this problem from an empirical perspective. A recent study of 149 individuals (90 females, 59 males) of ages 6 to 81 in southern Ontario, Canada, produced a detailed plot of tibia lead as a function of age for the general population (*20*). The relation between tibia lead and age was not significantly different between males and females. Based on these results, the intercept of the temporal axis occurs at approximately 5 years of age, and this age was selected as a starting point for the revised CBLI integration. Inspection of similar data sets gathered for a variety of studies (*2,7–9,13,21,22*) generally indicate x-axis intercepts of $t > 5$ years. The 5-year starting point therefore represents a conservative approach to the present investigation of systematic bias.

A further consideration is the need for an estimate of the background level of lead exposure as a function of time. The concentration of lead in blood for a given nonoccupationally exposed individual will depend on a variety of factors, and even producing a mean estimate over a large population is no simple matter. For guidance in this respect, one may refer to blood lead measurements from the second and third National Health and Nutrition Examination Surveys (NHANES) performed in the United States. The median blood lead level for American males surveyed from 1988 to 1991 (n = 6,051) was 3.8 µg/dl, whereas the median for

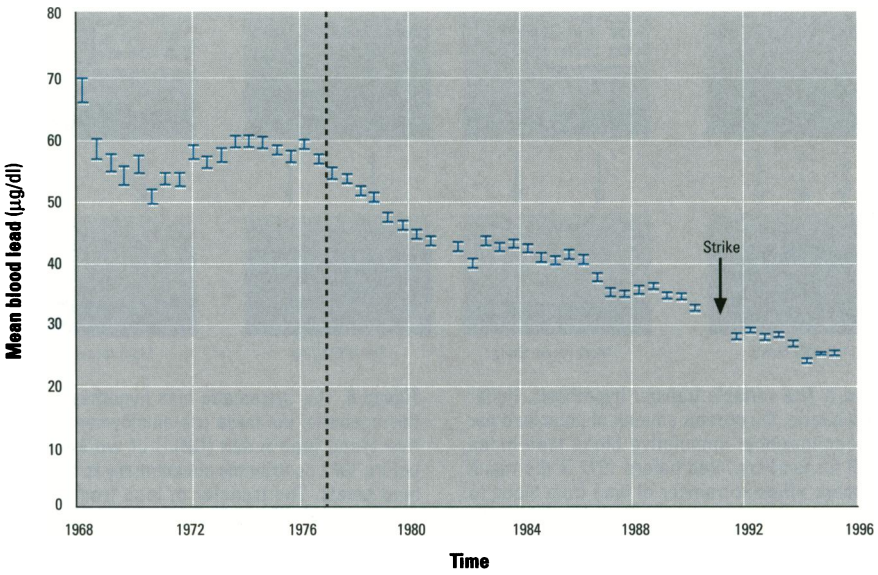

Figure 5. Mean blood lead of smelter workers as a function of time. The bars represent standard errors of the mean. Note the steady decrease in blood lead levels from 1977 on and the gap in data during the recent labor disruption. The dashed line indicates the point of division by time of hire.

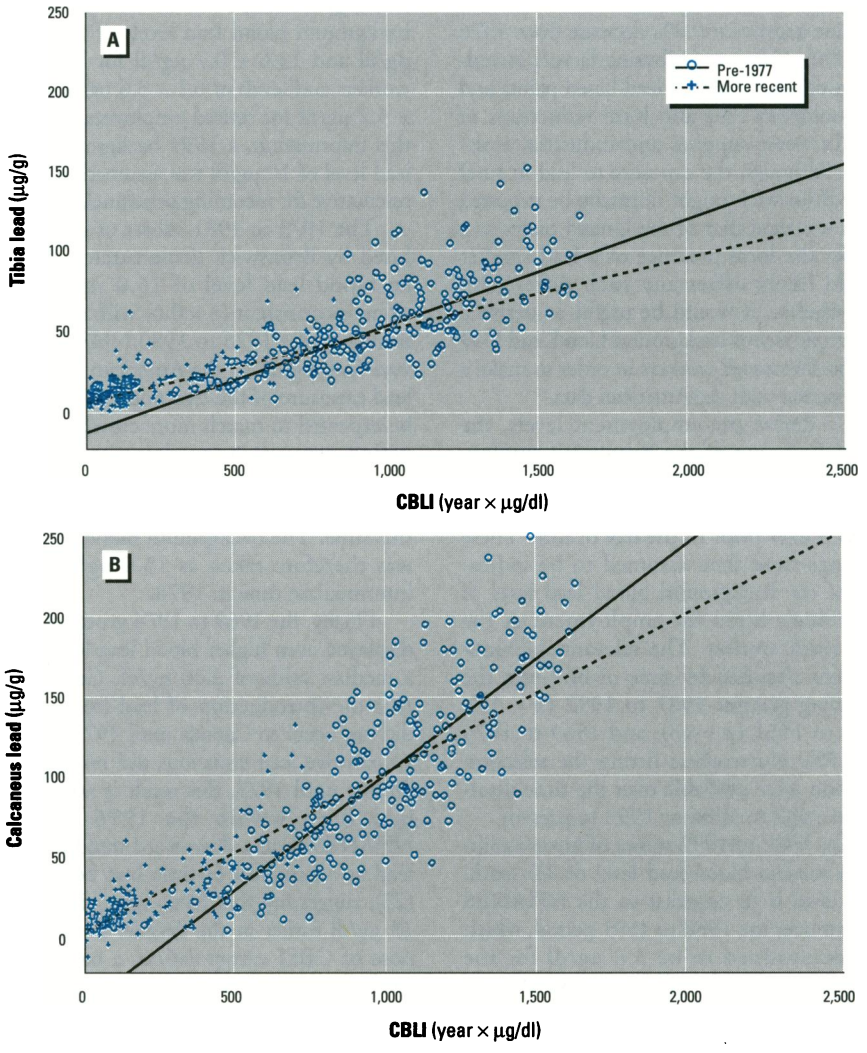

Figure 6. Bone lead concentration as a function of cumulative blood lead index (CBLI), with data divided by time of worker's hire. (A) Tibia as bone site of interest; (B) calcaneus as bone site of interest.

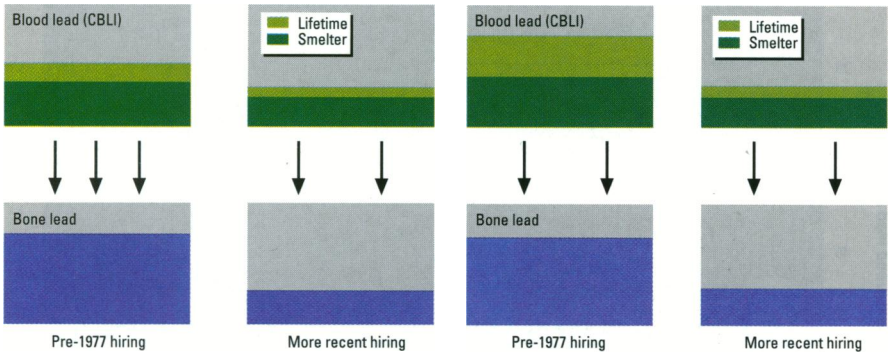

Figure 7. The variable transfer hypothesis. Under this scenario, the greater amount of bone lead per unit occupational cumulative blood lead index (CBLI) for workers hired before 1977 is the result of a more efficient transfer of lead from blood to bone during the early years of smelter operation (as represented by the arrows).

Figure 8. The systematic bias hypothesis. Under this scenario, the large pre-employment cumulative blood lead index (CBLI) of workers hired before 1977 contributes substantially to their bone lead levels. The transfer of lead from blood to bone is relatively constant over time (as represented by the arrows).

those examined between 1976 and 1980 (n = 4,895) was 15.0 µg/dl (*17*). This significant decrease in blood lead level was predominantly a result of the steep reduction in lead as a gasoline additive (99.8% decrease from 1976 to 1990). Other contributing factors included lower production of lead-based paints and lead-soldered cans and local reductions of lead in water supplies and industrial emissions. Although the exposure to lead in rural New Brunswick might normally be expected to be less than that of the United States as a whole, the local presence of a lead smelter would likely offset any such difference. Nonetheless, it would be useful to derive a pre-employment background blood lead level for the Brunswick workers in order to make a comparison with the American data.

To derive pre-employment levels, the blood lead data of the Brunswick employees were scanned for any measurements that occurred either on the day of hire or up to 3 days prior to the day of hire. These readings were then assumed to be indicative of the background blood lead level of individuals hired for employment at the Brunswick smelter. The relevant individuals were classified by time of hire into the following groups: 1987 to 1992 (n = 17), 1975 to 1981 (n = 13), and 1969 to 1974 (n = 38). No workers fitting the selection criterion were available over the time intervals of 1982 to 1986 or 1993 to present.

The 1987 to 1992 subset of hirees exhibited a median blood lead level of 8.0 µg/dl. This level is in contrast to the NHANES median over the 1988 to 1991 period, which was determined to be 3.8 µg/dl for the American male. The offset is statistically significant (p<0.02), with the elevated levels exhibited by the Brunswick hirees possibly a consequence of hiring local area residents. The relative proximity of a residence to a lead smelter would presumably introduce such individuals to a slightly elevated lead exposure. This finding reflects those of the 1991 readings discussed above, which suggested background blood lead levels of 13.6 ± 0.8 µg/dl and 13.6 ± 0.7 µg/dl for Brunswick workers and levels of 6.1 ± 3.6 µg/dl and 9.2 ± 4.2 µg/dl for retired employees. Based on this information, a 1991 background blood lead level of 10 µg/dl was assumed to be representative for incoming personnel.

The 1975 to 1981 subset of individuals hired by Brunswick demonstrated a median blood lead level of 16.0 µg/dl. This value is consistent (p = 0.6) with that determined by the 1976 to 1980 NHANES survey: 15.0 µg/dl for the American male. The lead exposure of the two populations might be expected to match more closely over this period because the smelter's contribution would not be as dominant a source because of the widespread use of leaded gasoline at this time. The background blood lead level was therefore taken as 15.0 µg/dl for an intermediate time in 1978.

Finally, the 1969 to 1974 group of hirees displayed even higher blood lead levels, with a median value of 22.0 µg/dl. Considering that the introduction of lead-free gasoline did not occur in Canada until 1972 and that automotive lead emissions did not begin to decline until 1973, this result is not surprising. Even within the 1976 to 1980 NHANES data, a downward trend in blood lead as a function of time had been noted (*23*), suggesting that levels were higher than 15 µg/dl earlier in the decade. For the purpose of CBLI extrapolation, a background level of 20 µg/dl was assumed to apply at all times before 1972. In summary, the blood lead background for incoming workers, which was used to calculate the presmelter component of CBLI, was established as 10 µg/dl in 1991 and at all times that followed, 15 µg/dl in 1978, and 20 µg/dl in 1972. A linear rate of change was applied between these three points of interest.

Revised CBLI results. Again dividing the Brunswick workers into groups consisting of those hired before and after 1977, the lifetime (revised) CBLI data was compared with the tibia and calcaneus lead concentrations. A linear fit to the tibia lead versus revised CBLI data for those hired before 1977 (Fig. 9A) now produces the following equation:

$$T = (0.0584 \pm 0.0048)\,CBLI - (24 \pm 7)$$
$$[n = 209; r^2 = 0.42; p<0.001].$$

Similarly, the calcaneus lead-revised CBLI data (Fig. 9B) yields:

$$C = (0.127 \pm 0.008)\,CBLI - (76 \pm 11)$$
$$[n = 209; r^2 = 0.58; p<0.001].$$

For workers hired more recently, the best fit linear equations relating the same variables are as follows (Fig.9A,B):

$$T = (0.0406 \pm 0.0029)\,CBLI - (7 \pm 2)$$
$$[n = 158; r^2 = 0.56; p<0.001];$$

and

$$C = (0.0842 \pm 0.0054)\,CBLI - (26 \pm 4)$$
$$[n = 158; r^2 = 0.61; p<0.001].$$

The differences between the slopes of the relations for those hired before 1977 and those hired after this time remain clearly significant, with p<0.01 for the tibia and p<0.001 for the calcaneus. This result implies that the original differences observed in slope (with the CBLI integrated only over smelter employment time) were not artifacts of a systematic bias in CBLI calculation. Consequently, the possibility of a variable transfer efficiency of lead from blood to bone becomes more attractive. Potential explanations for this variation include age-related effects, changing blood lead concentrations resulting from changing exposure conditions, and whether or not the lead exposure involves a strong endogenous component.

Discussion

Endogenous release of lead. The relation between bone lead concentration and the resulting endogenous exposure to lead is one of great importance. Instances of acute lead poisoning may occasionally have some component originating from lead stores in bone. Knowledge of the link between bone lead and endogenous exposure to lead allows an objective assessment of this contribution. This relation also provides a baseline from which to consider the effects of

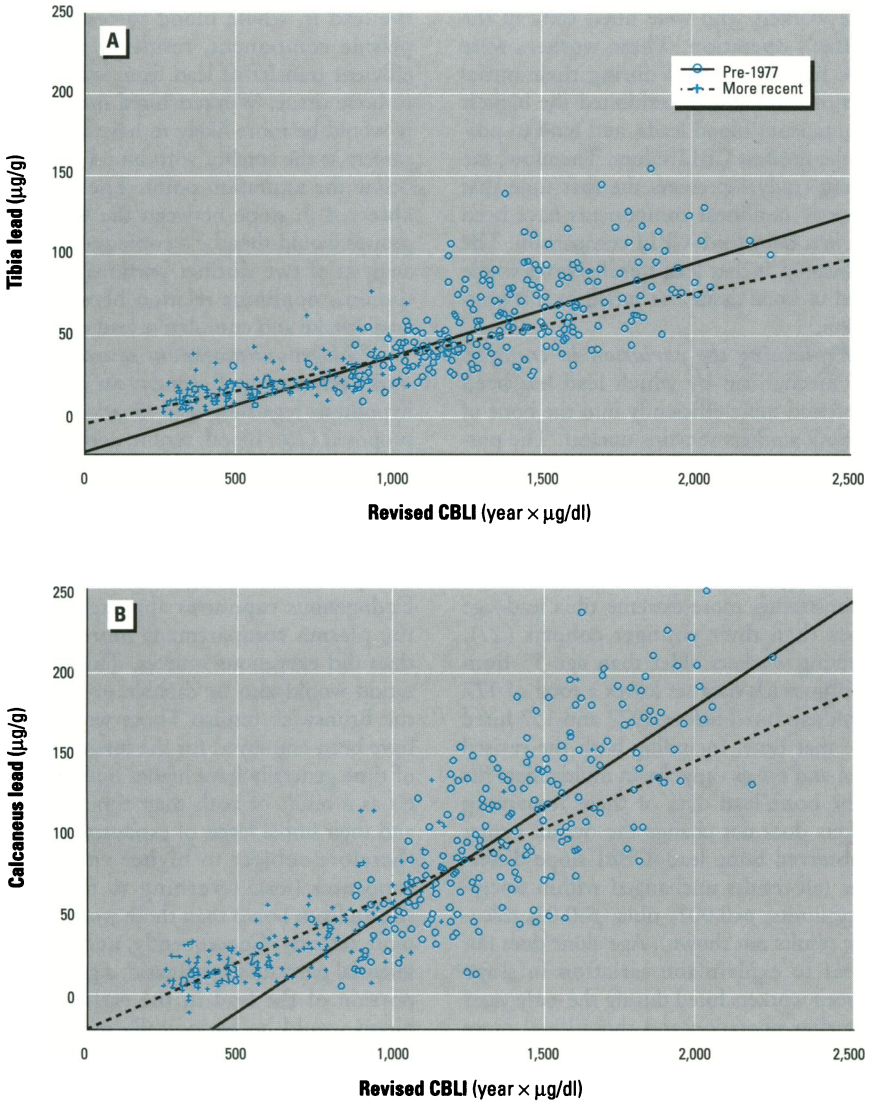

Figure 9. Bone lead concentration as a function of revised cumulative blood lead index (CBLI), with data divided by time of worker hire. (A) Tibia as bone site; (B) calcaneus as bone site of interest.

bone lead stores on exposure during times of elevated bone turnover, such as pregnancy, lactation, and following menopause (*24,25*). The contribution from bone-released lead is particularly significant for retired workers of lead-related industries.

The present study indicates that the relation between blood lead and tibia lead for workers who have been removed from their occupational lead exposure may be characterized by a linear relation of slope 0.136 ± 0.014. This result is consistent with analogous studies involving retired workers from a lead smelter in Sweden and two lead acid battery factories in Finland:

$$BPb = 0.133T + 5.3$$
$$[n = 30; r_s^2 = 0.25; p<0.01];$$

and

$$BPb = 0.138T + 7.7$$
$$[n = 16; r^2 = 0.59; p<0.001]$$

(*7,8*). When the blood lead levels of returning Brunswick workers were plotted against calcaneus lead concentrations, a more shallow slope of 0.0776 ± 0.0074 was derived. Again, this value is much the same as those determined from the European research:

$$BPb = 0.0622C + 4.0$$
$$[n = 30; r_s^2 = 0.22; p<0.01];$$

and

$$BPb = 0.0721C + 6.9$$
$$[n = 16; r^2 = 0.45; p<0.01]$$

(*7,8*).

Therefore, it seems that the contribution to blood lead from bone stores at any instant in time is similar for all occupationally exposed populations, regardless of whether active or retired workers are considered. The implication is that, at least for the samples examined to date, age-related variations in bone turnover are not a dominant factor in the endogenous exposure of male lead workers. The circumstances that allowed this analysis to be performed on such a large population of active lead industry employees are not likely to prevail again in the near future. This may therefore represent the most precise currently feasible statement of the bone lead–endogenous lead exposure relation.

The y-intercept values, which essentially indicate the expected blood lead levels in the absence of any bone lead stores, are higher in the current study—at 13.6 ± 0.8 µg/dl and 13.6 ± 0.7 µg/dl. Although uncertainties in the y-intercepts are not provided in the European studies, the consistency of their results, together with the small uncertainties in our data, suggest that this offset is significant. This may be representative of a higher background exposure to lead for the Brunswick workers relative to their Scandinavian counterparts. Alternatively, this elevation may be an artifact of the inclusion of some workers in the study whose blood lead samples were not taken immediately upon their return to work. However, when the sample was limited to those workers whose blood lead levels were recorded on the day of their return, the results were unchanged within uncertainty limits.

As a final check for the link between bone lead and endogenous exposure, the slopes and intercepts of linear fits to plots of blood lead against bone lead were derived for the 14 participating retired workers. For the tibia as the bone site of inspection, the slope was found to be 0.162 ± 0.051 and the y-intercept was 6.1 ± 3.6 µg/dl. The calcaneus yielded a slope of 0.0593 ± 0.0305 with an intercept of 9.2 ± 4.2 µg/dl. Although the uncertainties are much larger in this relatively small sample of retirees, it is evident that the slope results are consistent with both those of the retired European workers and those of the post-strike Brunswick employees. The y-intercepts appear to be of an intermediate magnitude. To verify these trends, a larger sample of retired workers would be desirable .

Bone lead at different sites. The positive correlations found between calcaneus lead and tibia lead in both active and retired smelter workers may be compared with those identified by other recent investigations. As displayed by Figure 2, the Brunswick results suggest a fairly tight relationship between the

two variables, with a slope of 1.70 ± 0.04 and an intercept of 0.6 ± 2.2 μg/g describing the active workers' calcaneus lead against tibia lead regression. The small population of retired workers provided similar results; the slope was determined to be 1.70 ± 0.29 and the y-intercept was 16.7 ± 20.7 μg/g. The fact that calcaneus lead concentrations tend to be elevated relative to those of tibia lead indicates the absorption is more rapid at this particular bone site. This result is characteristic of both the greater volume of blood delivered per unit time to trabecular bone and its more rapid metabolic turnover. Comparisons of bone lead concentration at these two sites have been performed for various other occupationally exposed populations in the past. With tibia lead concentration treated as the independent variable, slopes have ranged from 1.17 (*10*) to 2.50 (*9*), with y-intercepts extending from -14.7 μg/g (*9*) to 48.0 μg/g (*8*). Although a fair range of results are represented in the literature, the Brunswick relation is certainly consistent in suggesting how much the calcaneus lead concentration will typically exceed that of the tibia in a given exposed worker.

Accumulated lead body burden. The bone lead–CBLI relations derived from a small sample of former Brunswick employees were suggestive of a different slope relative to active workers. The results from these retired individuals were similar to those from active workers hired before the year 1977. These trends, however, were not significant statistically. A sample size of n = approximately 100 retired smelter workers would be required to substantiate these findings. It is interesting to note that Erkkilä et al. (*7*) also identified higher bone lead–CBLI slopes among a group of retired lead battery workers.

Workers hired during the initial years of smelter operation were found to have been exposed to higher levels of lead. It was speculated that the nonlinear nature of the active worker bone lead–CBLI plots could be a consequence of employment history. The possibility that the uptake of lead per unit exposure can vary in occupationally exposed individuals was probed by dividing the Brunswick workers by time of hire.

The relation between bone lead and the CBLI for lead industry workers is normally assumed to be of a linear nature. The application of linear regressions to the two subsets of Brunswick workers (those hired before 1977 and those hired more recently) revealed distinctly different relations between bone lead and CBLI. This difference emerged regardless of whether the occupational CBLI was entered as the independent variable, or whether a more rigorous lifetime CBLI was introduced. Greater bone lead to CBLI ratios were identified for those workers who were hired early in the smelter's operation. These workers were more heavily exposed during their initial years of employment, exhibited the highest instantaneous blood leads, and tend to possess the greatest CBLI values. Therefore, the present study represents the first time that distinctly nonlinear components have been seen in a bone lead–CBLI comparison. The implication is that lead transfer from whole blood to bone tissue has varied in this population.

Explaining the variation in transfer. The mechanism by which lead has been transferred more efficiently into the bone of the early workers remains unclear. The possibility that age is a factor in lead kinetics has been suggested by at least two X-ray fluorescence studies of environmentally exposed populations (*21,22*). Specifically, males of age 55 or greater were identified as demonstrating more extreme tibia lead–age slopes than their younger cohorts (*21*). Rejecting workers older than age 55 from the Brunswick data set leaves a total of 177 individuals hired before 1977 and 157 hired since that time. Including both the revised CBLI and age as variables in multivariate fits to the bone lead data of these remaining workers does not change the overall nature of observed bone lead–CBLI slope differences (all results unchanged within uncertainty limits; $p<0.001$, tibia; $p<0.01$, calcaneus; results not shown). Age alone does not appear to explain the variation in slope between workers hired during the early years of smelter operation and those hired more recently. The fact that Brunswick workers hired before 1977 were likely to receive higher exposure to lead than those hired since that time implies that any difference in uptake could simply be related to exposure level. Two distinct explanations involving lead kinetics are consistent with this hypothesis and will be examined below.

Blood lead level and saturation of red cell binding. There has been much speculation regarding the existence of a saturation level for lead binding in red blood cells. Models of lead kinetics normally assume the transport of lead throughout the body to be governed by the plasma component of whole blood (*26–28*). At elevated blood lead levels, a distinctly nonlinear relation between serum lead and blood lead has been observed (*29–31*), suggesting a gradual saturation of binding sites in red blood cells beyond which more lead becomes biologically available. This mechanism is consistent with the results of the present study. Early smelter workers exhibited relatively high blood lead levels and may have frequently surpassed such a saturation point. This would cause a higher proportion of the lead in whole blood to reside in the plasma component, resulting in a more efficient transfer of lead from whole blood to bone tissue. Workers hired more recently would be more likely to have spent their careers at the smelter with blood lead levels below the saturation point. The difference observed in slope between the two hiring groups would then be a consequence of the analysis of two distinct portions of a continuous, nonlinear relation between bone lead uptake and cumulative lead exposure.

Endogenous/exogenous sources of lead and partitioning. Recently, an alternative hypothesis regarding lead kinetics has been proposed (*10*). Blood, serum, and bone lead measurements from a population of battery recycling workers pointed to a differential partitioning of lead between plasma and blood, depending upon whether the source of exposure was endogenous or exogenous. Endogenous exposures appeared to favor the plasma compartment more strongly than did exogenous sources. This interpretation would also be capable of explaining the Brunswick results. Those workers who have been employed for the longest periods of time generally have higher bone lead levels as a result of both their time of service and their initial levels of exposure. They are therefore subject to higher endogenous exposures (lead returning to the bloodstream from bone) than those workers hired more recently. Consequently, under the differential partitioning scenario, a greater proportion of the lead in the early workers' blood would be biologically available for redistribution in the body.

In any case, the significant result remains: bone lead–CBLI relations show a more efficient transfer of lead to bone for those workers who have experienced the most extreme cumulative exposures. With bone lead acting as an indicator of overall body burden, the apparent variation in blood–bone transfer emphasizes the importance of the smelter's safety initiatives of the mid-1970s.

A secondary question that arises in light of this result is why similar nonlinear findings have not been apparent in previous investigations of lead industry workers. There are a number of factors that could conceivably differentiate this study from those it followed. Differences deal mainly with the quality of the data set available from the Brunswick survey. A total of 280 of the 367 participating active workers had complete blood lead records, dating to within one month of their initial hire. This represents 76% of the population and suggests that extrapolation was not an important feature for the majority of CBLI estimations. For those workers who did

require an extrapolation, the application of a routine, taking into account the temporal trend in their personal blood lead records, should have produced more accurate results than would an alternative approach. The large sample of workers involved, representing a wide distribution of CBLI and bone lead readings, is a further advantage. As a final note, the use of a revised X-ray fluorescence system (*6*) for these bone lead measurements resulted in the collection of a more precise data set than would have been previously possible.

From a broad perspective, it appears possible that at least some of the variation in bone lead–CBLI slopes exhibited between studies is a result of differences in lead exposure intensity. It is interesting to note that the largest tibia lead–CBLI slope results have been derived from those populations who have displayed the highest blood leads and CBLIs (See Table 1): smelter workers in Belgium (*15*) and retired Finnish battery plant employees (*7*). The lowest slopes have been observed from those workers with more moderate exposures: smelter workers in Sweden (*8*) and active Finnish battery plant workers (*7*).

As a gauge of long-term body burden, elevated bone lead readings are a cause for some concern. It will be interesting to see if a similar nonlinear relation is evident in future bone lead–CBLI results. The investigation of serum lead levels, in tandem with such a study, would help clarify the important kinetic modeling question of whether a saturation of lead binding sites occurs in red blood cells. Regardless of the mechanism, it remains significant that as a consequence of changing exposure conditions, individuals who have been working for the longest periods of time have also experienced an accelerated accumulation of lead body burden.

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